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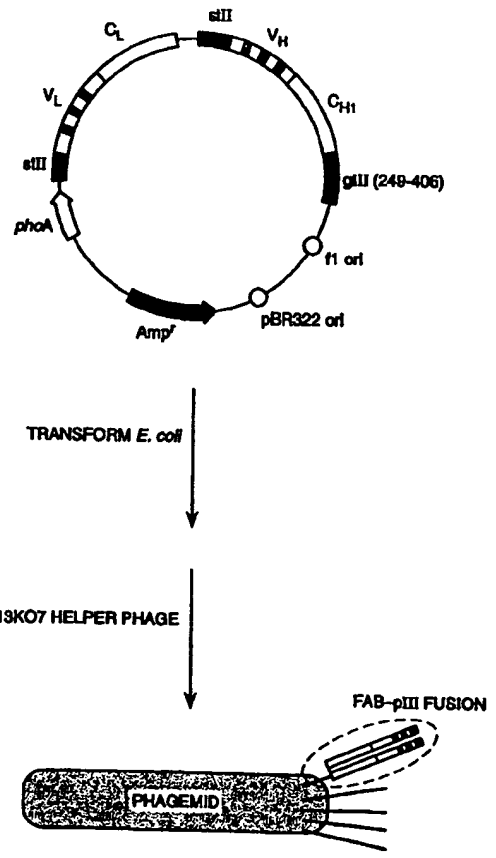
(54) Title: HUMANIZED ANTIBODIES AND METHODS FOR FORMING HUMANIZED ANTIBODIES

(57) Abstract

Described herein is a humanized antibody to vascular endothelial growth factor (VEGF). Also described herein is a method for rapidly producing and identifying framework mutations which improve the binding of humanized antibodies to their cognate antigens. In a preferred embodiment, non-human CDRs are grafted onto a human $V_{I}\kappa I$-$V_{H}III$ framework. Random mutagenesis of a small set of critical framework residues is also performed followed by monovalent display of the resultant library of antibody molecules on the surface of filamentous phage. The optimal framework sequences are then identified by affinity-based selection. Optionally, the selected antibodies can be further mutated so as to replace vernier residues which sit at the V_L-V_H interface by residues which match the non-human parent antibody. The methods described herein can be applied to any non-human antibody. Accordingly, humanized antibodies are provided.



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INTERNATIONAL SEARCH REPORT

Inte onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K16/22 C12N15/13 C12N15/63 C12N15/70 A61K39/395

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 22653 A (GENENTECH INC) 23 December 1992	3,11
Y	the whole document and specially: see SEQ.ID.N. 17 and 18 see page 5, line 24 - page 7, line 35 see page 9, line 22 - page 10, line 4; figure 5	1,2,9,10

Y	KIM ET AL.,: "Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo" NATURE, vol. 362, 1993, page 841 XP002013864 London, GB cited in the application see abstract	1,2,9,10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of theinternational search	Date of mailing of the international search report
18 September 1998	02/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

1

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